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Review Article

# The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management

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ABSTRACT

Hyper Immunoglobulin M syndrome (HIGM) is a rare primary immunodeficiency disorder characterized by low or absent levels of serum IgG, IgA, IgE and normal or increased levels of serum IgM. Various X-linked and autosomal recessive/dominant mutations have been reported as the underlying cause of the disease. Based on the underlying genetic defect, the affected patients present a variety of clinical manifestations including pulmonary and gastrointestinal complications, autoimmune disorders, hematologic abnormalities, lymphoproliferation and malignancies which could be controlled by multiple relevant therapeutic approaches. Herein, the epidemiology, pathogenesis, clinical manifestations, diagnosis, management, prognosis and treatment in patients with HIGM syndrome have been reviewed.

## 1. Introduction

Hyper-immunoglobulin M syndrome (HIGM) was first described in 1961 by Rosen et al. [1] and molecularly was defined in 1992 with a report of a mutation in the *CD40 ligand* (*CD40L*) gene [2]. This syndrome is also known as immunoglobulin class switch recombination (Ig-CSR) deficiencies. Ig-CSR deficiencies are a group of rare inherited primary immunodeficiency disorders (PIDs) characterized by low or absent serum levels of IgG, IgA and IgE, whereas the IgM concentration is either normal or increased [3,4].

To date, in addition to *CD40L* mutations in several genes responsible for B cell signaling, Ig-CSR, somatic hypermutation and DNA repair mechanism involved in presentation of HIGM phenotype, including *CD40L*, *CD40*, nuclear factor-kappa-B essential modulator (*NEMO/IKKγ*), inhibitor of kappa light chain gene enhancer in B cells, alpha (*IκBα*), nuclear factor kappa-B subunit 1 (*NKFB1*), activation-induced cytidine deaminase (*AICDA*), uracil-DNA glycosylase (*UNG*), ataxia telangiectasia mutated (*ATM*), post meiotic segregation increased 2 (*PMS2*), MutS Homolog 6 (*MSH6*), MutS Homolog 2 (*MSH2*), *INO80*, the gene encoding Nibrin/Nijmegen breakage syndrome 1 (*NBS1/NBN*), meiotic recombination 11-Like Protein A (*MRE11*), recombination activating gene 2 (*RAG2*), phosphatidylinositol 3-kinase catalytic delta (*PIK3CD*), phosphatidylinositol 3-kinase regulatory subunit 1 alpha (*PIK3R1*), tumor necrosis factor receptor superfamily member 13B (*TACI/TNFRSF13B*), inducible T-cell costimulator (*ICOS*), *CD19*, B cell-activating factor receptor (*BAFF-R/TNFRSF13C*), LPS Responsive Beige-Like Anchor Protein (*LRBA*), phospholipase C gamma-2 (*PLCG2*), Bruton tyrosine kinase (*BTK*) and signaling lymphocyte activation molecule-associated protein (*SAP*) [2,5–10]. Although less frequent cases of the HIGM syndrome with autosomal recessive inheritance have been reported in previous studies, the X-linked Hyper-IgM syndrome (X-HIGM), which is caused by *CD40L* mutations, is the most common form of HIGM and accounts for about 65–70% of all cases [3,11]. HIGM predisposes affected individuals to recurrent and prolonged infections including opportunistic infections, neutropenia, autoimmune disease and cancer [12]. Immunoglobulin replacement is an effective treatment for decreasing chronic infections in patients with HIGM, however in patients with combined immunodeficiency hematopoietic stem cell transplantation (HSCT) should be considered [13].

Patients with HIGM syndrome could have distinct clinical infectious complications based on the genetic characteristic and exact type of the syndrome, which makes it a challenge for clinicians and researchers. Majority of autosomal forms of HIGM are presented as a typical humoral PID; however the X-linked and autosomal dominant forms show the spectrum of clinical manifestations similar to the combined immunodeficiency disorders [14]. Early diagnosis and appropriate

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management of HIGM patients would be performed more efficiently by knowing the clinical phenotypes along with associated immunological and genetic parameters.

## 2. Epidemiology

The prevalence of HIGM varies in different ethnicities across the world. According to US X-HIGM registry, the prevalence of X-HIGM was approximately 1 in 1,000,000 live births from 1984–1993 [15]. The estimated frequency of CD40L deficiency is 2:1,000,000 in males [15]. Although there are few data available on the frequency of AICDA deficiency, this disorder is estimated to affect less than 1:1,000,000 individuals [16]. Globally, all forms of HIGM constitute 0.3–2.9% of all patients with PIDs. In 2014, a multicenter report on PID by Jeffrey Modell Foundation (JMF) indicated ~880 HIgM patients (2.3% of 37,532 antibody deficient patients and 1.2% of all 77,193 PID patients). In this report CD40L deficiency ranked as 28$^{th}$ frequent type of PID (372 patients, 42.2% of all HIgM patients, 272 patients from US) worldwide. Of note, CD40 deficiency (92 patients, 71 patients from US) was more common genetic defect compared to AID deficiency (81 patients, 71 patients from US), however majority of the CD40 deficient patients have not been reported in details [17]. A study of 7430 PID patients from the European Society for Immune Deficiency (ESID) demonstrated that 3.08% of PID patients enrolled had CSR defects, the most prevalent being CD40L deficiency with a frequency of 1.16% [18]. According to the national registry in Spain, the incidence rate of all forms of HIGM is 1 per 20 million live births which X-HIGM represents about 65–70% of all cases [19]. Studies are inadequate to provide racial and ethnic data regarding X-HIGM incidence. The US X-HIGM registry reported the racial background of 75 patients, as 52 of the patients were white, 12 were black, 9 were Asian, 1 was both black and Asian, and 1 was white and Asian [15].

A retrospective study of the Registry of the ESID on 56 affected males showed a 20% survival rate in individuals aged ~25 years [20]. The US X-HIGM Registry reported that 11 out of 61 surviving patients were aged 20 years or older [15]. The leading cause of death was pneumonia, encephalitis or malignancy. Other patients died of liver failure secondary to sclerosing cholangitis and cirrhosis. We reported the prevalence of HIGM in the third report of the national registry in Iran in 28 cases (3.8 %) [12]. In a national study of morbidity and mortality of 38 Iranian HIgM patients, 10-years survival rate was 67.8% and the most common cause of death in HIgM patients is respiratory failure [21].

## 3. Pathogenesis

Defective interaction of CD40L-CD40 between CD4$^+$ T cells and antigen presenting cells (APCs) is known as the underlying cause of HIGM syndromes. CD40L-CD40 interaction is the first step in B cell stimulation for class switch recombination (CSR) and somatic hyper mutation (SHM) resulting in the generation of various Ig isotypes [22–24]. All forms of HIGM syndromes are characterized by markedly reduced serum levels of switched immunoglobulins with normal to increased serum IgM as a result of defective CSR [25]. HIGM patients indicate decreased numbers of isotype switched memory B cells along with normal numbers of total B cells [26].

Except mutation in *CD40* and *CD40L* genes, HIGM syndrome could also be due to mutations in genes involved in signaling pathway and DNA repair mechanism as above mentioned [4,5,7,14,27–32] (Fig. 1). Except for the patients with *PMS2* defects, ataxia telangiectasia (A-T) and *UNG* deficiency and those with autosomal dominant mutation of *AICDA* who have intact SHM, all other HIGM patients have defective CSR and SHM [5,31,33,34]. Characteristics of mutations in genes affected in HIGM phenotype are explained in the following sections.

### 3.1. CD40L and CD40 mutations

The most prevalent type of HIGM is the X-linked CD40L deficiency accounting for almost 65–70 % of all cases, exclusively observed in male subjects [24,35]. The *CD40L* gene is located at X chrmosome [36,37] which encodes CD40L (CD154), a member of tumor necrosis factor (TNF) family made-up of 3 functional domains: intracellular, transmembrane and extracellular [38]. More than 100 unique mutations including single amino acid substitutions, truncations, in-frame or out-of-frame deletions, nonsense, missense, insertion and splice-site mutations have been reported among X-HIGM patients (http://structure.bmc.lu.se/idbase/CD40Lbase). These mutation mostly affect the extracellular domain, resulting in a defective geometrical folding of CD40L or preventing the CD40L/CD40 binding [6,15,39–42]. Abnormalities in the promoter region of the *CD40L* gene [43] have been also identified to be responsible for X-HIGM [3]. Defective T cell costimulation in CD40L-deficiency leads to combined T- (cellular) and B-cell (humoral) immunodeficiency [24,44].

CD40, a unique receptor of CD40L, is a member of the TNF receptor family that is expressed on APCs (B cells, monocytes, macrophages and dendritic cells). CD40 deficiency is one of the autosomal recessive types of HIGM syndromes [44,45]. Reported biallelic mutations in the gene encoding CD40, consist of a single amino acid change in a highly conserved area of an extra-cellular cysteine-rich domain, a 6-bp deletion in exon 4 and a cryptic splice site resulting in skipping of exon 5 [29,46]. Therefore there are many underreported patients with CD40 deficiency according to IDbase (http://structure.bmc.lu.se/idbase/CD40base) and JMF global report [17]. Similar to CD40L deficiency, defects in CD40 also result in combined immunodeficiency.

### 3.2. AICDA and UNG mutations

B cell intrinsic defects including defects of *AICDA* and *UNG* genes comprise two other autosomal recessive types of HIGM syndromes. AID and UNG enzymes have a crucial role in CSR and SHM processes [23,47]. AID generates deoxyuracils by deaminating deoxycytosine in the switch regions of the immunoglobulin heavy chain genes during CSR [48], afterwards, UNG removes deoxyuracils from DNA as a part of generating double-strand breaks during Ig isotype switching, initiating DNA repair pathway [49,50]. *AICDA*, the gene encoding AID and to date, amino acid substitutions, premature stop codons and deletions mostly in exon 3 have been reported as the homozygous mutations of *AICDA* responsible for autosomal recessive HIGM affecting both CSR and SHM [14,30]. Moreover, a heterozygous mutation in the C terminal end of *AICDA* has been recently reported as the autosomal dominant type of HIGM syndromes with intact SHM [34].

A compound heterozygous mutation of two frameshift variations, a homozygous frameshift in exon 2 and a homozygous amino acid substitution (F251S) in *UNG* gene, all affecting glycosylase domain, have been reported as mutations responsible for HIGM [31]. UNG deficient patients present with normal numbers of CD19$^+$ B cells, CD27$^+$ memory B cells and normal T-cell immunity as well as AID deficient patients [25].

### 3.3. PI3KR1 and PI3KCD mutations

PI3K(s) are a family of enzymes that participate in cellular functions such as cell growth, proliferation, differentiation and survival. Class 1 PI3K enzymes are expressed in leukocytes and formed by a catalytic and a regulatory subunit. CD40/CD40L interaction activate PI3K directly or via GTP-ase RAC leading to increase reactive oxygen species generation and controlling the expression of CD40 [51]. Recently heterozygous gain-of-function mutations in the genes encoding p110-δ catalytic (mainly affecting C2 and kinase domains) and p85-α regulatory (only affecting ISH2 domains) subunits which are respectively responsible for activated PI3K-delta syndrome (APDS) and SHORT syndrome, have

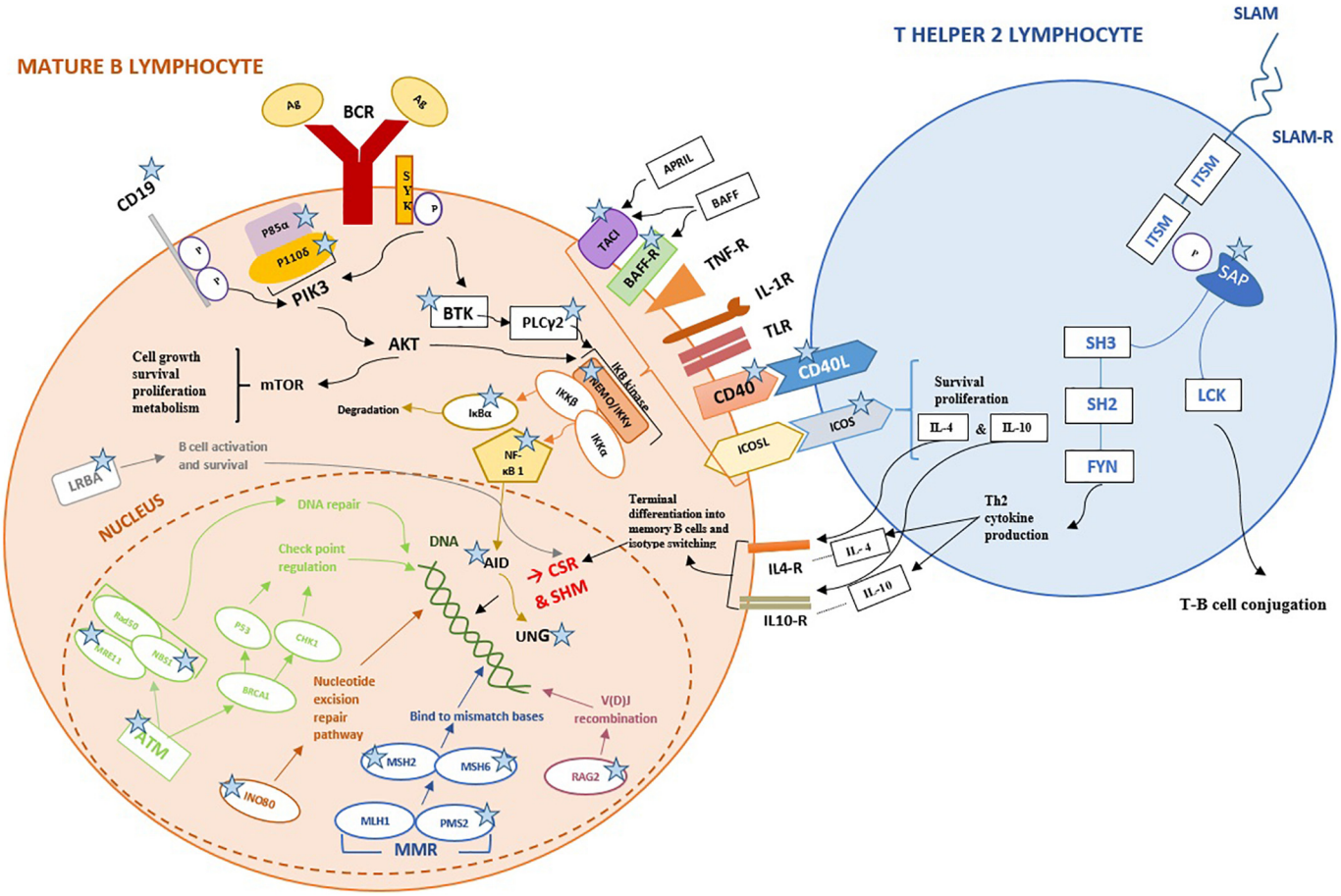


**Fig. 1.** Mutated genes and the affected pathways involved in HIGM syndrome. The mutated factors are tagged with stars. P indicates phosphorylation.

been reported to be associated with HIGM phenotype [6,52–59].

### 3.4. NEMO and IKBA mutations

Proteasomal degradation of IκB kinase (IKK) complex (consisting of 2 catalytic proteins, IKKα and IKKβ) is provided by its phosphorylation performed by NEMO, the regulatory subunit of IκB complex, allowing nuclear translocation of NF-κB for downstream CD40/CD40L signaling and PI3K activation [60]. Mutations in 2 genes can lead to NF-κB signaling defects (*NEMO* and *IKBA*) affecting the epigenetic control of protein profile expression required for CSR in activated B cells [61].

X-linked Anhidrotic (hypohydrotic) Ectodermal Dysplasia with Immunodeficiency (EDA-ID) is considered as a syndrome associated with HIGM caused by mutations in *NEMO/IKK*γ gene. *NEMO* gene is X-linked and also EDA-ID exclusively affects males. A point mutation in the C-terminal portion of the gene is reported to be the predominant mutation in the affected patients leading to an abnormal expression of multiple enzymes required for antibody switching such as AID and UNG [44,62–65]. Autosomal dominant mutations of *IKBA/IκBα*, another crucial factor in the process of downstream CD40 signaling have been reported in a few patients presenting with HIGM phenotype [66–68]. Mutations of *IKK*γ and *IκBα* both result in blockage of NF-κB release into the nucleus interfering with NF-κB and downstream CD40 signaling. Thus, those patients with autosomal dominant mutations of *IKBA* resemble EDA-ID patients with *NEMO* mutations [41].

### 3.5. DNA repair genes mutations

PMS2, MSH2, MSH6 and INO80 are a component of mismatch repair machinery involved in the CSR-induced generation of double-strand DNA breaks in switch regions and abnormal formation of switch junctions [5,10]. *MRE11* and *NBN* genes encode proteins which make a complex for detection and recruitment of DNA repair machinery during CSR and activate ATM protein. Nijmegen breakage syndrome (NBS) is an autosomal recessive chromosomal instability syndrome accompanied by immunodeficiency in the result of NBN deficiency, predominantly due to a truncating 5 base-pair (bp) deletion. Both humoral and cellular immunity are defective in the affected patients [32,69]. MRE11 deficiency and ATM deficiency present as a syndromic PID, Ataxia–telangiectasia (A-T), which is a neurodegenerative disease associated occasionally with HIGM. During the last decade, we and others have reported A-T cases, in whom Ig CSR defect was indicated prior to the neurological symptoms [7,70–72]. In our previous study performed in 2017, we showed that 21.2% of AT patients revealed Ig CSR defect [73].

### 3.6. Other mutations

HIGM phenotype could be observed in some antibody deficiency disorders including mutations in *BTK* gene responsible for X-linked agammaglobulinaemia (XLA) disease and *SAP/SH2D1A* gene associated with X-linked lymphoproliferative (XLP) disease [42,74–76]. It is supposed that the remaining patients with increased IgM levels who do not have mutations affecting above mentioned genes, may be common variable immunodeficiency (CVID) patients with mutations in *TNFRSF13B*, *TNFRSF13C, ICOS*, *CD19, LRBA, NFKB, VAV1* and *PLCG2* genes which could lead to increased levels of serum IgM through defective B-cell maturation as a result of dysfunctional CSR and SHM. Other genes that are not yet identified could also be the underlying cause of HIGM syndromes [8,42,76,77].

## 4. Clinical manifestations

The majority of patients with HIGM syndrome present with a broad spectrum of clinical manifestations even with a same genetic defects [3]. They usually develop symptoms in infancy and second year of life, including susceptibility to recurrent bacterial and opportunistic infections. Furthermore, these patients are prone to pulmonary complications, gastrointestinal manifestations, autoimmune disorders, hematologic abnormalities, lymphoproloferation and malignancies.

### 4.1. Infections

The most prominent clinical feature observed in CD40L/CD40 deficiencies is severe infection. The infections are caused by bacteria, viruses, fungi and parasites. In a North American cohort study of 79 X-HIGM, sinopulmonary infections (pneumonia 81%, upper respiratory infections 49%, otitis media 43% and sinusitis 43%) were described as the most frequent clinical manifestations among the affected patients [15]. In another report of 56 X-HIGM patients by the European group, infections were the leading clinical manifestations with upper and lower respiratory tract infections being the most common complication among them [20]. Other studies have also suggested sinopulmonary infections as the leading feature among X-HIGM patients [6,24,40,41,78–83]. Recurrent sinopulmonary infections are also presented in AID deficiency [40,84–86]. Patients with APDS also suffer mainly from respiratory and gastrointestinal infections and less frequently with bronchiectasis, skin infections and deep abscesses [6,52–59].

Defects in CD40L/CD40 pathway in HIGM patients result in a combined immune deficiency with a defect in immunoglobulin isotype switching, subsequently susceptibility to opportunistic infections [44,87]. According to European and US cohort, pathogens causing opportunistic infections in these patients include *Pneumocystis (carinii) jiroveci*, *Bartonella*, *Herpes family viruses*, *Cryptosporidium parvum* (in exposure to contaminated drinking water [88]), *Histoplasma* [89–91], *Mycobacterium avium* [92], *Salmonella dublin* [93], *Cryptococcus neoformans*, *Leishmania* [94] and *Candida albicans* [95,96]. Enteroviral meningoencephalitis has also been presented among X-HIGM patients [88,97]. In contrast to the CD40L- and CD40-deficient patients, the susceptibility to opportunistic infections is much less frequent in AID- and UNG-deficient patients [30,31,85], as a result of unaffected T-cell immunity [98]. In a study of 29 patients with AID deficiency, central nervous system infections including *Haemophilus influenzae* meningitis, *Herpes simplex virus (HSV)* encephalitis and meningitis with no identified microorganism were diagnosed [85]. Main germs in APDS patients are also *Streptococcus pneumonia* and *H.influenza,* although susceptibility to cytomegalovirus (CMV), Epstein–Barr virus (EBV) and Human papillomavirus (HPV) also have been observed.

Respiratory tract complications due to recurrent infections are commonly affected organ in patients with both X-linked and autosomal recessive types of HIGM [81,87,88]. Pneumonia is the most common cause of pulmonary complications among these patients [40,79,81,83,99]. In a cohort study of 56 X-HIGM patients, 87.5% of the patients suffered from upper respiratory tract infections (URTI), followed by lower respiratory tract infections (LRTI) developing bronchiectasis (82.5%), parenchymal (51.8%) and interstitial (39.3%) infections. Interstitial pneumonia caused by *P.carinii*, CMV and adenovirus infections, *C.neoformans* lung infection and Mycobacterial pneumonia (caused by bacillus Calmette-Guèrin, *Mycobacterium bovis* or atypical Mycobacterium) are the other reported RTIs [20]. The most common pathogens responsible for pneumonia according to a cohort study of 28 X-HIGM Latin American patients were *P.carinii*, CMV, *Pseudomonas aeruginosa*, Streptococcus spp., parainfluenza virus type II, Aspergillus spp., *M.pneumonia* and *Serratia marcescens* [99]. According to a report by Singleton et al., recurrent pneumonia predisposes the X-HIGM patients to bronchiectasis [100]. Thus, early diagnosis and management of recurrent/persistent pneumonia can help to prevent the development of bronchiectasis which limits the success of HSCT [101].

Infectious gastrointestinal manifestations are the second most common feature of the X-HIGM patients presenting with recurrent or protracted diarrhea commonly due to organisms such as *C.parvum*, *Giardia lamblia*, Salmonella spp. and *Entamoeba histolytica* [6,15,20,78,79]. Other features include proctitis [2], oral ulcers associated with neutropenia caused by defective CD40/CD40L interactions and granulopoiesis [6,78,102–104], stomatitis [88], gingivitis and perianal ulcers [20]. Sclerosing cholangitis may occur in associatuion with *C.parvum* infection which may be the result of chronic diarrhea [15] and could lead to cirrhosis with a risk of cholangiocarcinoma [105,106] and liver, pancreas or biliary tree tumors [6,105]. Chronic hepatitis (due to Hepatitis B virus, Hepatitis C virus and CMV [97]) and liver cirrhosis with hepatic failure or severe cholestasis requiring liver transplantation [20] are other infectious gastrointestinal complications in HIGM. Gastrointestinal diseases are also presented less severely in AID-deficient patients [40,86,88].

### 4.2. Autoimmunity and inflammatory disorders

The presence of autoimmune diseases in HIGM patients suggests the improper maintenance of tolerance among these patients [97,107]. Autoimmunity occurs in all types of HIGM syndromes with variable presentations based on the underlying genetic defect [97]. Autoimmune complications frequently manifest in patients with AID (25%), NEMO (23%), and CD40L (20%) defects [108]. In a study of 29 AID-deficient patients, 6 cases manifested with autoimmunity or inflammation: diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombocytopenia, Crohn's disease and chronic uveitis [85]. In a cohort study by Levy et al., inflammatory disorders such as seronegative arthritis, inflammatory bowel disease, thrombocytopenia and autoimmune hemolytic anemia were identified [20]. Coombs positive hemolytic anemia and nephritis [107], autoimmune hepatitis, hypothyroidism and discoid lupus erythematous, inflammatory bowel disease (IBD), and rheumatoid arthritis (RA) are the other autoimmune complications manifested among patients with defective CD40/CD40L signaling [44,91,109,110]. Other uncommon autoimmune diseases including autoimmune retinopathy have also been indicated in association with CD40L deficiency [111]. Management of autoimmunity in HIGM patients, needs special considerations because dysregulations and dysfunctions of the immune system along with persistent inflammation impair the process of diagnosis and treatment [112].

### 4.3. Lymphoproliferation and malignancies

Patients with AID and UNG deficiency and APDS syndrome usually present with enlarged lymph nodes and hepatosplenomegaly during early childhood due to over-activated germinal centers [14,31,40,55,88]. In a study of 29 AID-deficient patients, lymphoid hyperplasia was characterized by hyperplasia of peripheral lymph nodes in 45% as well as mesenteric lymph nodes, mediastinal lymph nodes, spleen, liver and tonsils [85]. Lymphoproliferation significantly increases the risk of lymphoma in patients with APDS [6,52–59,113].

Lymphadenopathy is a clinical feature manifested among X-HIGM patients [20]. Of note affected patients also have a higher risk of developing lymphoma [105]. However, adenocarcinoma of the gastrointestinal tract [114] particularly liver malignancies such as hepatocellular carcinoma, bile duct carcinoma and biliary tree tumors are common complications presented in adolescent and young adults which account for approximately 25% of mortality associated with X-HIGM [15,24,105,115]. Although neuroendocrine carcinoma is a rare tumor, patients with CD40L/CD40 deficiency are predisposed to develop this tumor [15,115]. Neuroendocrine carcinoma is mostly localized to the appendix and colon, but it can also locate at extra-appendicular sites [116]. Following the X-HIGM patients may lead to earlier detection of

neuroendocrine carcinoma [115]. Cooke et al. reported that CD40L-positive tumors have both lower grade and stage. Moreover, Hussain et al. noted that the expression of CD40L in transitional cell carcinoma of the bladder (TCC) is associated with better outcome [117]. Some studies suggest that the CD40L may be a potential anti-tumor agent [118–121]. ATM, NBS1 and PMS2 are involved in DNA repair mechanisms, thus patients with genetic defects in the mentioned DNA-repair components are susceptible to malignancies mainly lymphoma [5,7,122].

### 4.4. Other complications

Osteopenia is another clinical feature which is observed in affected patients. Spontaneous rib fractures without antecedent trauma have been manifested among X-HIGM patients. CD40L-deficient patients have significantly lower bone mineral density (BMD) as a result of osteoclastogenesis and increased osteoclastic activity. It is suggested that defective INF-γ secretion by the activated T-cells due to defective T-cell/APC interaction may be responsible for osteopenia among the affected patients [15,123].

Major clinical manifestations and the related underlying genetic defects with uncommon HIGM phenotype are summarized in Table 1.

## 5. Diagnosis of HIGM syndromes

### 5.1. Clinical diagnosis

Generally, detection of immunoglobulin levels, distribution of lymphocyte subsets, detection of CD40 and CD40L markers on activated $CD4^+$ T cells and B cells, family history and genomic sequencing should be taken into account for the diagnosis of HIGM syndrome. Based on the latest European Society for Immunodeficiencies (ESID) criteria, HIGM syndrome is diagnosed by at least one of the following: increased susceptibility to infections, immune dysregulation, cytopenia, malignancy, and affected family member. In addition, significant decrease of IgG, normal or elevated IgM, exclusion causes of hypogammaglobulinemia. Although ESID criteria also recommend excluding DNA repair defects from HIGM by exclusion of profound T-cell deficiency and ataxia telangiectasia (http://esid.org/Working-Parties/Registry/Diagnosis-criteria) all other syndromic PID and combined immunodeficiency should be considered in the diagnosis of HIGM disease using an unbiased molecular diagnosis [8]. Positive family history with early death in male members may lead to earlier diagnosis of X-linked syndromes like CD40L or NEMO deficiencies and parental consanguinity may suggest an autosomal recessive form of the HIGM [8,78].

### 5.2. Detailed immunologic and laboratory diagnosis

Some differential clue during the process of diagnosis could be helpful including neutropenia in X-HIGM patients, increased radiosensitivity in patients with patients with DNA repair defects and elevated serum level of alpha fetoprotein in ATM deficiency. AID- and UNG-deficient patients have normal numbers of $CD27^+$ memory B cells, however, patients with CD40 and CD40L deficiency have remarkably reduced numbers of switched memory B cells and normal counts of peripheral blood B cells [14]. Peripheral blood T cells, $CD4^+$ and $CD8^+$ T cell subsets and T cell proliferation are all within normal limits in AID- and UNG-deficient patients [2,20,26,29,124], but antigen-induced T cell proliferation is defective in some of X-HIGM patients [125]. Expression level of activated PI3K signaling products (e.g phosphorylated AKT and phosphorylated S6) can be diagnostic in patients with APDS [6,52–59].

The lack of CD40L expression on activated $CD4^+$ T cells [126] and platelets [127] is typically assessed by activation of T cells [23] and peripheral blood mononuclear cells [128] with phytohaemagglutinin (PHA), phorbol myristate acetate [23] and ionomycin [128] followed by flow cytometric analysis [23]. However, it is not a reliable diagnostic tool for all CD40L-deficient patients mainly with hupomorphic missense mutaitons [3]. Flow cytometric screening method fails to identify patients even with in-frame deletions/insertions [83]. Thus, detection of the soluble CD40-Ig fusion protein, on the other hand, identifies the majority of the patients with X-HIGM [42]. Cytofluorimetric analysis can also be used for demonstrating the lack of CD40 expression at B cell surface. However, the possibility of false-positive results should be regarded, as monoclonal antibodies against CD40 may also recognize the expressed mutant CD40 at cell surface or even expressed CD40 with defective function due to heterozygous mutations of *CD40* gene all resulting in a HIGM phenotype [129]. Some patients with CVID demonstrate decreased or absent CD40L expression which may be mistaken for X-HIGM, therefore genetic evaluation should be complemented to this evaluation [130]. This can be performed by amplification of *CD40L* exons and the flanking intron regions by primer sequences and PCR or using a targeted gene panel or high-throughput sequencing [80,115]. The later method can molecularly identified other types of HIGM as well as AID and UNG deficiencies and APDS within a same time-frame.

## 6. Management of HIGM syndromes

There are multiple therapeutic approaches to control the complications of HIGM syndromes, including immunoglobulin replacement therapy, antimicrobial therapy, monitoring of the patients for liver function, G-CSF (Granulocyte-colony stimulating factor), CD40-agonist therapy, immune-suppressive therapy, HSCT and gene therapy.

Infections as the major complications in HIGM syndrome are treated and controlled by conventional courses of antibiotics [131]. According to the susceptibility of CD40L/CD40-deficient patients to opportunistic infections, they should receive prophylactic *P.carinii* treatment with oral trimotheprim sulfamethoxazole or intravenous/inhaled pentamidine [5]. Prolonged courses of antibiotics and antifungal agents may be required for severe conditions. Patients with protracted diarrhea positive for cryptosporidium parasite need antibiotic treatment (nitazoxanide and azithromycin), nutritional support or parenteral nutrition [132], close follow-up and infection management [133]. Intravenous or subcutaneous immunoglobulin replacement therapy should be started at the time of diagnosis. It is suggested that regular infusion of 400–600 mg/kg/month of preparations [134] could result in decreased severity and frequency of infections [2], reduced antibiotic usage, decreased frequency of hospitalization, improved pulmonary function, and improved growth and quality of life [135]. In case of chronic diarrhea and severe pulmonary complications (e.g. bronchiectasis) the dose of immunoglobulin replacement should be adjusted using through level measurement [136,137].

Immune-suppressive therapy could be considered as an approach for patients with autoimmune and inflammatory disorders. In a cohort study of AID-deficient HIgM patients, 6 out of 29 patients suffered from autoimmune and related inflammatory disorders which were well controlled in 3 of the patients with immunosuppressive therapy including corticosteroid therapy, cyclophosphamide and cyclosporine [85]. Lymphoproliferation of APDS patients can be controlled with Rapamycin, inhibitor of downstream PI3K effector mTOR pathway, but it seems less effective on bowel inflammation and cytopenia of these patients [113]. Regarding neutropenia, which is commonly observed in the patients with CD40L deficiency, it could effectively be treated with GCSF [138].

According to the importance of liver diseases' prevention, careful monitoring of the liver and biliary tract is important which may require ultrasound examinations and biopsies [25]. Regularly monitoring for liver enzymes and eosinophil counts by applying sensitive methods such as PCR-based amplification of stool DNA and microscopy of bile fluid [139] is very important. Sclerosing cholangitis and *cryptosporidium* infection are highly associated [129] and both can diminish the rate of a successful HSCT [133]. In this regard, it is recommended hygienic

**Table 1**
Characteristics of reported genes and clinical manifestations in patients with hyper IgM syndrome.

| No | Reported genes | Inheritance | Chromosome | Kind of mutations | Clinical manifestations | References |
|---|---|---|---|---|---|---|
| 1 | *CD40L* | X-linked | Xq26.3 | single amino acid substitutions<br>truncations<br>in-frame deletions<br>out-of-frame deletions<br>nonsense<br>missense<br>insertion<br>splice-site mutations | opportunistic infections caused by pathogens like: *Pneumocystis jiroveci* pneumonia, *Cryptosporidium* species, *cytomegalovirus* and *Candida albicans*<br>recurrent sinopulmonary infections<br>gastrointestinal infections<br>chronic diarrhea<br>CNS infections<br>gastrointestinal tumors (hepatic/pancreatic carcinoid-bile duct, hepatocellular and gastroenteropancreatic neuroendocrine carcinoma-adenocarcinoma)<br>sclerosing cholangitis<br>liver cirrhosis<br>neutropenia<br>autoimmunity<br>osteopenia | [6,15,20,24,39–42,78–83,95,104–107,111,114,115,123,139,149,154,155] |
| 2 | *CD40* | autosomal recessive | 20q13.12 | amino acid change<br>missense<br>deletion<br>splice site mutation | opportunistic infections caused by pathogens like: *Pneumocystis jiroveci* pneumonia, *Cryptosporidium*<br>chronic diarrhea<br>sclerosing cholangitis<br>liver cirrhosis<br>neutropenia | [29,44–46,95,151] |
| 3 | *AICDA* | autosomal recessive<br><br><br><br>autosomal dominant | 12p13.31 | missense<br>amino acid substitutions<br>deletions<br>mutation in the C terminal end of the gene | sinopulmonary infections<br>gastrointestinal infections<br>lymphadenopathy<br>lymphoid hypertrophy<br>autoimmunity<br>splenomegaly | [14,30,34,40–42,84–86,156] |
| 4 | *UNG* | autosomal recessive | 12q24.11 | amino acid substitution<br>deletion<br>frameshift mutation | sinopulmonary infections<br>lymphadenopathy<br>lymphoid hypertrophy<br>autoimmunity | [31,42,84] |
| 5 | *NEMO/IKKγ* | X-linked | Xq28 | point mutations<br>frameshift mutation | ectodermal dysplasia (dry scaly skin, conical-shaped teeth, absence of eccrine sweat glands)<br>recurrent infections<br>autoimmunity | [42,62–65,76,157] |
| 6 | *IκBα/IKBA/ NFKBIA* | autosomal dominant | 14q13.2 | missense<br>nonsense | anhidrotic ectodermal dysplasia<br>recurrent infections<br>chronic diarrhea<br>hepatosplenomegaly | [66–68] |
| 7 | *PMS2* | autosomal recessive | 7p22.1 | deletions | colonic adenocarcinoma<br>bacterial infections<br>Café-au-lait spots | [5] |
| 8 | *ATM* | autosomal recessive | 11q22.3 | nonsense<br>deletion | gait abnormalities- head and trunk swaying- wobbliness with walking-ocular and cutaneous telangiectasia- progressive cerebellar ataxia-abnormal eye movements-dysarthria<br>recurrent respiratory infections<br>lymphoma<br>radiosensitivity | [7,158–161] |
| 9 | *NBN/NBS1* | autosomal recessive | 8q21.3 | deletion | progressive and severe microcephaly<br>mental retardation<br>recurrent respiratory infections<br>malignancy<br>radiosensitivity | [32,69,162,163] |

(*continued on next page*)

**Table 1** (*continued*)

| No | Reported genes | Inheritance | Chromosome | Kind of mutations | Clinical manifestations | References |
|---|---|---|---|---|---|---|
| 10 | *MSH6* | autosomal dominant and recessive | 2p16.3 | missense<br>nonsense<br>deletion<br>insertion | hereditary non-polyposis colorectal cancer<br>mismatch repair cancer syndrome<br>lymphoma<br>Turcot syndrome | [164] |
| 11 | *MSH2* | autosomal dominant and recessive | 2p21-p16 | nonsense<br>deletion<br>missense<br>frameshift mutation | hereditary non-polyposis colorectal cancer<br>mismatch repair cancer syndrome<br>Muir-Torre syndrome<br>leukemia<br>lymphoma | [165] |
| 12 | *MRE11* | autosomal recessive | 11q21 | nonsense<br>missense | ataxia-telangiectasia-like disorder (ATLD) | [23] |
| 13 | *INO80* | autosomal recessive | 15q15.1 | missense | recurrent bacterial infections<br>recurrent URT infections | [166] |
| 14 | *PIK3CD* | autosomal dominant | 1p36.22 | missense<br>amino acid substitution | APDS<br>respiratory infections<br>lymphadenopathy<br>lymphoma<br>hepatosplenomegaly | [52–54,59] |
| 15 | *PIK3R1* | autosomal dominant | 5q13.1 | splice site mutation | SHORT syndrome<br>respiratory infections<br>lymphadenopathy<br>lymphoma<br>hepatosplenomegaly | [55–58] |
| 16 | *TNFRSF13B* | autosomal dominant and recessive | 17p11.2 | missense<br>insertion<br>frameshift mutation | recurrent sinopulmonary<br>gastrointestinal infections<br>lymphoma | [42,167–169] |
| 17 | *ICOS* | autosomal recessive | 2q33.2 | deletion | recurrent sinopulmonary<br>gastrointestinal infections | [42,77,170,171] |
| 18 | *CD19* | autosomal recessive | 16p11.2 | insertion | recurrent sinopulmonary<br>gastrointestinal infections<br>pneumonia | [42,172] |
| 19 | *TNFRSF13C* | autosomal recessive | 22q13.2 | deletion | recurrent sinopulmonary<br>gastrointestinal infections | [42,173] |
| 20 | *LRBA* | autosomal recessive | 4.q31.3 | nonsense | recurrent respiratory infections<br>lymphadenopathy<br>autoimmunity | [174] |
| 21 | *NFKB1* | autosomal dominant | 4q24 | splice-donor-site mutation<br>frameshift mutation<br>deletion | common variable immunodeficiency (CVID)<br>respiratpry tract infections<br>pneumonia<br>lymphadenopathy | [175,176] |
| 22 | *PLCG2* | autosomal dominant | 16q23.3 | deletion<br>missense | familial cold autoinflammatory syndrome-3 (FCAS3)<br>autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation (APLAID) | [177,178] |
| 23 | *RAG2* | autosomal recessive | 11p12 | missense | B cell negative severe combined immunodeficiency (SCID)<br>Omenn syndrome | [179–182] |
| 24 | *BTK* | X-linked recessive | Xq22.1 | nonsense<br>missense | recurrent infections<br>lymph node hypoplasia | [42,75,76] |
| 25 | *SAP/SH2D1A* | X-linked recessive | Xq25 | nonsense | XLP<br>fulminant infectious mononucleosis<br>lymphoma | [74,183] |

measures including the use of boiled or filtered water and administration of anti-*cryptosporidium* drugs could be applied for prevention of this parasite infection [25,129]. A liver transplant can be effective for the patients with liver failure such as sclerosing cholangitis and cirrhosis [140].

Despite the infection management among the X-HIGM patients, the morbidity and mortality rates are high among the patients, thus HSCT is believed to be the mainstay of therapy, especially for those with a full-match donor [20,101]. However, it seems to be less effective for autosomal recessive CD40-deficient patients, since it restores CD40 expression only for hematopoietic stem cell–derived cell lineages and not for other CD40-expressing cell types [25]. It has been shown that pre-existing hepatic [129] and pulmonary complications [23] (e.g. bronchiectasis [141]), mismatched unrelated donor, reactivation of cryptosporidium and grade 2–4 graft versus host disease (GVHD) [142] limit the success and can increase the risk of fatal outcome post-transplantation. Therefore, using more sensitive techniques for careful detection of cryptosporidium carriage and infection [129,133], monitoring the liver status using biochemical analysis and ultrasound [133] and administration of methylprednisolone and cyclosporine-A for GVHD-prevention [81] can lead to the better management of high-risk patients and improved outcomes. HSCT is a method of choice in major DNA repair defects presenting with combined immunodeficiency but not syndromic PIDs.

The success of gene therapy in the treatment of X-linked severe combined immunodeficiency disease (X-SCID) and adenosine deaminase deficient (ADA) SCID is a stimulus for the treatment of other immune deficiency diseases including HIGM syndromes [143–146]. Up to now, gene therapy for HIGM syndromes seems to be more complicated than that of X-SCID, as the expression of the *CD40L* gene is highly regulated, current methods of gene transfer result in constitutive gene expression, which may be harmful [3,147].

## 7. Prognosis

Prognosis of HIGM syndromes is highly related to the underlying molecular defect. Earlier management with immunoglobulin replacement therapy and antibiotic prophylaxis could improve the quality of life in patients by reducing the incidence of life-threatening infections. However, it is not effective in the prevention of hepatic and hematologic complications, including cancers [20]. According to previous studies, the overall prognosis among CD40L-deficient HIGM patients is poor, with an overall survival rate of 28.2% at age 40 years in one study and an average of 20% survival by age 25 years in another study with liver disease is a significant predictor of overall survival [15,40,41,83,105,148,149], nevertheless allogeneic HSCT before the onset of severe liver disorders can cure the disease [150], HLA-identical donor and liver transplantation in end-stage chronic liver disease [140], as well as early age at transplantation [148,149], are associated with better prognosis and survival of these patients.

Outcomes of HSCT in CD40-deficiency HIGM is not clearly obvious, as a result of the rarity of CD40-deficiency and lower numbers of CD40-deficient patients who have been treated with HSCT, however end-organ damage reduces the possibility of successful HSCT, thus associated with a higher mortality rate among these patients. Nevertheless, it is recommended to consider HSCT for CD40-deficient patients with the HLA-identical donor as severe infections and liver damage could lead to the poor prognosis of the CD40-deficient patients same as CD40L-deficient ones [151,152]. The only available curative option for APDS patients are also HSCT with positive outcome in 87.5% of patients [113]. In contrast to CD40L- and CD40-deficiency with defective cellular and humoral immunity, other forms of HIGM syndromes have a better prognosis as a result of intact cellular immunity and better protection against the infections [153].

## 8. Conclusion

HIGM phenotype could be observed in different monogenic immunodeficiency disorders, demonstrating the importance of molecular investigations for genes responsible for the CSR defects. The major prevalent genes involved in patients with HIGM phenotype include CD40L, CD40 and AICDA, however defect of other genes also can be helpful for targeted treatment and adjutant managements particularly in APDS and DNA repair defects. Detection of the underlying causes could be involved in better diagnosis and management of this disease. Altogether, the presence of various clinical and immunologic manifestations and prognosis in patients with HIGM indicates that it is necessary to identify the exact pathogenesis punctually at the time of diagnosis.

## Conflicts of interest

The authors declare that they have no conflict of interest.

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